Views and Reviews

Intracranial Angioplasty and Stent Placement After Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial: Present State and Future Considerations*

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ABSTRACT

OBJECTIVE

The results of prematurely terminated stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) due to excessively high rate of stroke and death in patients randomized to intracranial stent placement is expected to affect the practice of endovascular therapy for intracranial atherosclerotic disease. The purpose of this report is to review the components of the designs and methods SAMMPRIS trial and to describe the influence of those components on the interpretation of trial results.

METHODS

A critical review of the patient population included in SAMMPRIS is conducted with emphasis on "generalizability of results" and "bias due to cherry picking phenomenon." The technical aspects of endovascular treatment protocol consisting of intracranial angioplasty and stent placement using the Gateway balloon and Wingspan self-expanding nitinol stent and credentialing criteria of trial interventionalists are reviewed. The influence of each component is estimated based on previous literature including multicenter clinical trials reporting on intracranial angioplasty and stent placement.

RESULTS

The inclusion criteria used in the trial ensured that patients with adverse clinical or angiographic characteristics were excluded. Self-expanding stent as the sole stent, technique of prestent angioplasty, periprocedural antiplatelet treatment, and intraprocedural anticoagulation are unlikely to adversely influence the results of intracranial stent placement. A more permissive policy toward primary angioplasty as an acceptable treatment option may have reduced the overall periprocedural complication rates by providing a safer option in technically challenging lesions. The expected impact of a more rigorous credentialing process on periprocedural stroke and/or death rate following intracranial stent placement in SAMMPRIS such as the one used in carotid revascularization endarterectomy versus stenting trial remains unknown.

CONCLUSION

The need for developing new and effective treatments for patients with symptomatic intracranial stenosis cannot be undermined. The data support modification but not discontinuation of our approach to intracranial angioplasty and/or stent placement for intracranial stenosis. There are potential patients in whom angioplasty and/or stent placement might be the best approach, and a new trial with appropriate modifications in patient selection and design may be warranted.

Keywords: Intracranial atherosclerotic disease, intracranial angioplasty, intracranial stent, randomized clinical trial, stroke, death.

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Introduction: SAMMPRIS Trial

A previous National Institutes of Health (NIH) funded clinical trial Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) reported that patients with 70-99% intracranial stenosis had a high risk of stroke despite antithrombotic therapy and usual management of vascular risk factors.[1] Subsequently, a randomized phase III clinical trial (FDA IDE # G050157), Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS; NCT00576693), was initiated by NIH (1U01NS058728–01A1) to determine whether intracranial stent placement (using the Wingspan self-expanding nitinol stent) and intensive medical therapy is superior to intensive medical therapy alone.[2] The intent of the intervention was to prevent the primary endpoint (any stroke or death within 30 days after enrollment or stroke in the territory of the symptomatic intracranial artery beyond 30 days) during a mean follow-up of 2 years in high-risk patients with symptomatic stenosis of a major intracranial artery (http://www.clinicaltrials.gov/ct2/show/NCT00576693). The trial recruited patients with transient ischemic attack (TIA) or nondisabling stroke within 30 days prior to enrollment attributed to 70-99% stenosis of a major intracranial artery (middle cerebral, carotid, vertebral, or basilar arteries). The inclusion and exclusion criteria are provided in Table 1 (online only). The patients were randomized (1:1) to either intensive medical therapy alone or intracranial angioplasty and stent placement using the Gateway balloon and Wingspan self-expanding nitinol stent plus intensive medical therapy. Intensive medical therapy in both arms of the study consisted of aspirin 325 mg/day for entire follow-up, clopidogrel 75 mg/day for 90 days after enrollment, and aggressive risk factor management primarily targeting blood pressure <130/80 mm Hg and low density cholesterol concentration <70 mg/dL. The sample size of 382 patients in each group was chosen to detect a relative 35% reduction in the rate of the primary endpoint from stent placement based on the log-rank test with an alpha of .05, 80% power, and adjusting for a 2% loss to follow-up and a 5% crossover from the medical to the stent placement arm. Recruitment began in November 2008 and on April 11, 2011, based on the recommendation of the study's data safety monitoring board (DSMB) stopped enrollment after 451 (59%) of the planned 764 patients had been enrolled at 50 participating sites in the United States due to a higher risk of stroke and death in the stent treated patients.[3] At the time of the most recent DSMB review, 14% (95% CI 10.7–20.1) of the patients treated with angioplasty combined with stent placement experienced a stroke or died within the first 30 days after enrollment compared with 5.8% (95% CI 3.4–9.7) of patients treated with medical therapy alone, a highly significant difference. The 30-day rate of stroke or death in the intensive medical treatment arm was substantially lower than the estimated rate of 10.7% based on historical controls. In addition the 30-day rate in the stent treated patients was substantially higher than the estimated rate of 5.2-9.6% based on registry data. There were five stroke-related deaths within 30 days after enrollment, all in the stent placement arm. There was one nonstroke-related death in the medical arm within 30 days after enrollment. Beyond 30 days, the rates of stroke in the territory of the stenotic artery are similar in the two groups, but fewer than half the patients had been followed for 1 year.

The Principles for Interpretation of SAMMPRIS Results

Practitioners and institutions have to determine whether intracranial angioplasty and/or stent placement is a procedure that would be considered as an acceptable treatment option with or without local institutional review board oversight. One of the major concerns is that the results of the prematurely concluded trial are "overinterpreted" and institutions choose policies that are applied to patient populations that were not included in the trial. Two phenomena that need to be considered prior to deciding on policy changes include "generalizability of results" and "bias due to cherry picking phenomenon" as described in the subsequent sections.

In each study, the study sample is expected to be a representative subset of the eligible population targeted for application of the new procedure, as defined with rigorous inclusion and exclusion criteria. Narrow inclusion and exclusion criteria confine enrollment in the study to a smaller subset of patients with the disease but may impose limitations on the generalization of the results to the population with the disease. In addition, it is important to note that the inclusion and exclusion criteria may exclude a subset of patients who are of interest but for whom the risk/benefit ratio is deemed unacceptable, by investigators, institutional review board at participating centers, or the DSMB for the trial. A previous example of concerns regarding generalizability of results was observed in the International Subarachnoid Aneurysm Trial (ISAT) comparing embolization and surgical treatment in patients with ruptured aneurysms.[4] The overall in-hospital mortality was 6% in ISAT compared with the 26% in-hospital mortality observed for subarachnoid hemorrhage in the United States[5] and 22% in-hospital mortality in the Japanese Standard Stroke Registry Study.[6] These observations had suggested that patients treated in the ISAT had more favorable baseline clinical and procedural characteristics "cherry-picking phenomenon" compared with those observed in general population questioning generalization of results.

In studies in which a new procedure is being compared with medical treatment, the cherry-picking phenomenon may reduce the ability to detect meaningful differences in effectiveness, because of the low risk of recurrent events in the medical treatment group.[7] A major concern is that patients who are included in the clinical trial (eligible and randomized) represent those for whom a better clinical outcome could be expected because of the presence or absence of known prognostic factors or the investigators' experience, in comparison with patients who are eligible and not randomized.

Analysis of SAMMPRIS Patient Population

This section critically reviews the patient population included in SAMMPRIS with emphasis on "generalizability of results" and "bias due to cherry picking phenomenon."

Demographic Characteristics

The study included patients aged ≥30 years and ≤80 years. Patients aged 30-49 years were required to meet at least one additional criterion to increase the likelihood that the symptomatic intracranial stenosis is atherosclerotic. Exclusion of patients aged more than 80 years were similar to the Stenting of

Symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA),[8] Wingspan study,[9] Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT), and Apollo Stent for Symptomatic Atherosclerotic Intracranial Stenosis (ASSIST)[10] studies. In a pooled analysis from five centers including patients who underwent intracranial angioplasty and/or stent placement,[11] the rate of periprocedural stroke and/or death was 3-fold higher among patients aged greater than or equal to 80 years compared with those <80 years (20% vs 7%, $P = .11$). Therefore, such exclusion is expected to reduce the rate of periprocedural stroke and death in the stent treated patients.

Clinical Characteristics

(1) TIA versus ischemic stroke as index event: Patients with TIA or nonsevere stroke within 30 days of enrollment (defined using clinical and radiological criteria) were included. The VISSIT Intracranial Stent Study is using similar criteria. The qualifying event (TIA vs ischemic stroke) can influence the rate of periprocedural stroke and death in patients treated with intracranial stent. An analysis of NIH Multicenter Wingspan Intracranial Stent Registry Study[12] found that patients in whom the qualifying event was ischemic stroke had a higher rate of 1 month stroke and death compared with those with TIA (5% vs 16%, $P = .023$). This finding could not be reproduced in the European INTRASTENT registry[13] and another multicenter study.[14]

(2) Interval between index event and procedure: The ASSIST[10] study allowed inclusion of patients with ischemic symptoms within 90 days of enrollment. In one analysis, the rate of periprocedural stroke and death was similar among patients treated in less than 7 days from qualifying ischemic event and those treated ≥7 days after the qualifying event (4 of 33 vs 5 of 59, $P = .7$).[14] An analysis of NIH Multicenter Wingspan Intracranial Stent Registry Study[12,15] found that patients in whom stent placement was performed within 10 days from qualifying ischemic event was associated with a higher rate of 1 month stroke and death compared with those treated after 10 days (8% vs 17%, $P = .058$). Therefore, the data does not demonstrate a consistent relationship of periprocedural stroke and/or death with interval between index event and procedure.

(3) Neurological stability: Patients with progressive neurological signs within 24 hours prior to enrollment or thrombolytic therapy within 24 hours prior to enrollment were excluded in SAMMPRIS. Patients who are neurologically unstable have a high rate of periprocedural stroke and death (50% in one study).[16] Three of the 18 patients died–1 from intracerebral hemorrhage and 2 from cardiorespiratory failure. Similarly, exclusion of patients who received thrombolytics within the last 24 hours is expected to avoid the 5% rate of symptomatic intracranial hemorrhages seen in the SARIS (stent-assisted recanalization in acute ischemic stroke) trial performed in patients in the setting of acute stroke.[17] Overall, these inclusion criteria are either unlikely to affect or favorably influence the rate of periprocedural stroke and death.

(4) Recurrent ischemic events and antithrombotic treatment failure: The inclusion criteria of SAMMPRIS differed from the original trial that resulted in approval of the Wingspan stent.[9] The original trial only included patients who had failed antithrombotic therapy and experienced recurrent symptoms attributable to angiographically demonstrated intracranial stenosis ≥50%. All 45 patients enrolled into the study were taking antithrombotic medications at the time of entry. Of these, 38 patients (84%) were taking ≥1 antiplatelet medications (aspirin, clopidogrel, or ticlopidine), 19 (42%) were taking anticoagulants (heparin or warfarin), and 12 (27%) were taking a combination of antiplatelets and anticoagulants. Such a strategy of maximizing medical treatment and only using stent placement in the event of demonstrated failure may exclude patients with a lower risk of ischemic events with medical treatment alone and thus offer stent placement to those who are most likely to benefit from this procedure. However, a broad definition of antithrombotic treatment failure may not be adequate to identify high-risk patients. It should be noted that a post hoc analysis of WASID found no difference in the rates of stroke or vascular death or stroke in territory between patients who were receiving or not receiving antithrombotics at the time of their qualifying event.[18] Other studies have also not found a higher risk of recurrent stroke or death in patients who develop ischemic events despite use of antithrombotic agents.[19] Therefore, a narrow definition of antithrombotic medication failure limited to those patients who experience two or more ischemic events referable to the stenotic artery despite use of antithrombotic medication may be required to identify those who can benefit most from stent placement.

Angiographic Characteristics

(1) Angiographic severity of stenosis: The SAMMPRIS trial required that the qualifying event was related to 70-99% stenosis of a major intracranial artery. The VISSIT Intracranial Stent Study is using similar criteria. However, the SSYLVIA,[8] Wingspan[9] study, and ASSIST[10] studies included patients with stenosis measuring in severity 50-99%. The 1-month rates of periprocedural stroke and death were 6.6%, 4.5%, and 6.5% in the SSYLVIA,[8] Wingspan[9] study, and ASSIST[10] studies, respectively. However, four observational studies have found no difference in the periprocedural stroke and/or death among patients with 50-69% stenosis compared with those with ≥70%.[12–14,20]

(2) Anterior versus posterior circulation: SAMMPRIS also included both patients with target intracranial stenosis involving either the anterior or posterior circulation. The SSYLVIA,[8] Wingspan[9] study, VISSIT, and ASSIST[10] studies have all included patients with target stenosis located in either anterior or posterior circulation. An analysis of NIH Multicenter Wingspan Intracranial Stent Registry Study[12] found that patients in whom stent placement was performed for posterior circulation had a higher rate of 1-month stroke and death compared with those treated for anterior circulation (20% vs 6%, $P = .006$). A systematic review of 31 studies dealing with 1,177 procedures found that periprocedural complications were significantly higher in the posterior versus the anterior circulation (12.1% vs 6.6%, $P < .01$, odds ratio [OR]: 1.94, 95% confidence interval [CI]: 1.21 to 3.10).[21] Other observational studies have not found an association between the location of lesion (anterior or posterior circulation) and rate of periprocedural stroke or death.[13,14,22]

(3) Lesion length: The SAMMPRIS trial required that the target area of stenosis was in an intracranial artery that has a normal diameter of 2.00 to 4.50 mm with target area of stenosis is ≤14 mm. There has been variability in lesion length criteria for inclusion in various trials. The SSYLVIA[8] trial required that diameter with a reference vessel diameter is between 2.5 to 4.5 mm and lesion length ≤5 mm. The VISSIT Study requires the target artery diameter to be 2.0-5.0 mm and lesion length between 16 and 31mm. The ASSIST[10] trial required the lesion length to be <20 mm and normal arterial diameter adjacent to the stenosis range between 2.0 and 4.0 mm. The major issue is the length of the lesion and its relationship to periprocedural rate of stroke and death. The European INTRASTENT registry[13] reported that lesion lengths were <5 mm, 5-10 mm, and >10 mm in 21%, 63%, and 15%, respectively, in the treated patients. There was no significant effect of lesion length on periprocedural complications although lesions <5 mm appeared to have a lower rate (6%) than those with lengths 5-10 mm and >10 mm (13.6%). Another multicenter study found that 57% and 43% of the lesions treated were <7 mm and ≥7 mm without any relationship with periprocedural stroke or death.[14] The ASSIST[10] study reported that stent delivery failure was more frequent in lesions >10 mm compared with those <10 mm (25% vs 3%, $P = .04$) although no relationship could be demonstrated with periprocedural stroke and death.

(4) Proximal lesions: The SAMMPRIS trial excluded patients with tandem extracranial or intracranial stenosis (70-99%) or occlusion that is proximal or distal to the target intracranial lesion. The SSYLVIA[8] and ASSIST[10] studies excluded patients with stenosis ≥50% proximal or distal to the target lesion. A multicenter review suggested that endovascular treatment of patients with cervical and intracranial stenoses, although technically feasible,[23] appeared to be associated with a higher rate of 1 month

stroke and death.[24] Therefore, the angiographic characteristics of the patients included do not possess any unique features that would increase the rate of periprocedural stroke or death.

Analysis of Procedural Aspects of SAMMPRIS

Summary of Technical Aspects of Endovascular Treatment Protocol

The primary intervention of SAMMPRIS was intracranial angioplasty and stent placement using the Gateway balloon and Wingspan self-expanding nitinol stent (or any future Food and Drug Administation [FDA] approved iterations of the balloon, stent, or the delivery systems) to reduce the severity of stenosis to less than 50% with adequate coverage of the lesion. Patients who met the entrance criteria and consented were enrolled and, if randomized to stent placement, underwent stent placement as soon as possible after enrollment (optimally within 1-3 days).

All interventions were performed through a 6F access system. The targeted parent vessel was accessed with either a 6F-guiding catheter (Envoy or Envoy XB; Cordis Corporation, Miami, FL) or a 6F KSAW Shuttle-Select sheath system (Cook Medical Inc., Bloomington, IL). Heparinization was instituted to a targeted activated coagulation time (ACT) of 250 to 300 seconds. The lesions were primarily crossed with the Gateway angioplasty balloon and a Transcend 300-cm exchange-length .014-inch microwire (Boston Scientific, Natick, MA). In each case, the balloon diameter was sized to 80% of the "normal" parent vessel diameter. The balloon length was selected to match the length of the lesion. Angioplasty was typically performed with a slow, graded inflation of the balloon to a pressure of between 6 and 12 atm (recommended for at least 120 seconds). After angioplasty, the Wingspan delivery system was prepared and advanced over the exchange wire across the target lesion. The stent diameter was sized to exceed the diameter of the normal parent vessel by .5 to 1.0 mm. The stent length was selected to equal or exceed the length of the angioplasty balloon. In addition, the stent length was selected both to completely cover the entire diseased segment and to allow positioning of the proximal end of the stent so as not to preclude future endovascular access into the treated segment. The postprocedure stenosis defining technical success in the SAMMPRIS was set at less than 50%. The definition has varied in previous studies from $\leq$20% residual stenosis,[25] $\leq$30% residual stenosis,[26] but most commonly $\leq$50% residual stenosis.[9] Reporting standards for angioplasty and stent-assisted angioplasty for intracranial atherosclerosis stated that a reasonable definition of technical success would be reduction of stenosis grade $\leq$50%.[27]

Rationale for Wingspan Stent System

FDA had approved the Gateway balloon/Wingspan stent system (Boston Scientific) under a humanitarian device exemption (HDE).[9] The self-expanding nitinol Wingspan^{TM} Stent System was approved based on a safety study of 45 patients with intracranial stenosis $\geq$50%.[9] The mean severity of angiographic stenosis was reduced from 75% to 32% in 44 treated patients (lesion could not be traversed in 1 patient). The study reported a procedural success rate of 98%, and a 30-day rate of death or ipsilateral stroke of 4%. Among the 43 patients with 6-month follow-up, the rate of death or ipsilateral stroke was 7.0%. Further lesion reduction was observed in 24 of the 40 patients who underwent follow-up angiography at 6 months. In the US Wingspan registry,[28] intracranial stenosis treatment resulted in successful treatment in 99% in 78 patients with 82 intracranial lesions. There were 5 (6%) major periprocedural neurological complications including four deaths within 30 days. Follow-up imaging[29] demonstrated in-stent restenosis in 30% (n = 29) of the patients (more frequent within the anterior circulation); 8 were symptomatic (4 with stroke, 4 with TIA), and 15 requirement retreatment. In the NIH Multicenter Wingspan Intracranial Stent Registry,[15] technical success rate was 97% (<50% residual stenosis) among 129 patients with symptomatic intracranial stenosis $\geq$70%. The frequency of any stroke or death within 30 days or ipsilateral stroke beyond 30 days was 14% at 6 months. The frequency of $\geq$50% restenosis on follow-up angiography was 25% in 52 patients.

A More Permissive Policy Toward Primary Angioplasty as an Acceptable Treatment Option

There is some controversy whether primary angioplasty is equivalent to intracranial stent placement for intracranial stenosis. There are two potential strategies: (1) primary angioplasty as the sole modality; or (2) primary angioplasty considered an acceptable option in selected patients. In general, primary angioplasty is preferred for patients with small vessels (<2 mm diameter), long lesions that would require multiple stents (>12 mm), tortuous proximal vessels ($\geq$2 acute curves requiring traversing, judged by experience or trial), limited vessel length available distal to the lesion to allow stable placement of microwire, lesions located in the anterior cerebral, posterior cerebral or M2 segment lesions, or if a guide catheter cannot be placed in the distal vertebral artery or internal carotid artery. The existing data summarized below suggests that primary angioplasty is not inferior to stent placement in such scenarios and may reduce the overall periprocedural complication rates by providing a safer option in technically challenging lesions.

In a single center study,[30] the results of primary angioplasty (reserved for more complex lesions) were compared with stent placement for intracranial stenosis (concurrent unmatched controls). The 1-month stroke and/or death were 5% and 14% for angioplasty and stent treated patients, respectively. In a subsequent multicenter review,[31] outcomes were compared for 190 patients treated with 95 primary angioplasty procedures and 98 intracranial stents placements (total 193 procedures) in three tertiary care centers. The rate of stroke and/or death was 8.4% (8/95) in the angioplasty-treated group and 9.2% (9/98) in the stent-treated group (relative risk [RR] = .81, 95% CI, .28 to 2.4, P = .70) after adjusting for sex, age, and center. In a systematic review, Siddiq and colleagues[32] identified 69 studies (33 primary angioplasty-alone studies [1,027 patients] and 36 studies of angioplasty with stent placement [1,291 patients]) for the analysis. There were a total of 91 stroke-and/or-deaths reported in the angioplasty-alone–treated group (8.9%; 95% CI, 7.1-10.6%), compared with 104 stroke-and/or-deaths in the angioplasty-with-stent–treated group (8.1%; 95% CI, 6.6-9.5%) during a 1-month period (RR = 1.1; P = .48). A recent review of 74 patients from four institutions treated with primary angioplasty for intracranial

atherosclerotic disease[33] reported that the 30-day stroke/death rate was 5% (4 of 74; CI, 1.5% to 13%). However, inherent differences in the two groups might have affected the rates of clinical and angiographic end points independent of the treatment modality used.

Such evidence will continue to raise the question that a policy of mandatory stent placement may lead to higher periprocedural stroke and death without a clear evidence of incremental benefit.

Self-Expanding Stent as the Sole Stent for Treatment of Intracranial Stenosis

Intracranial stents are of two types: self-expanding and balloon expandable. The Wingspan stent system is a self-expanding, nitinol stent sheathed in a delivery system used in the SAMMPRIS. There are three balloon-expandable 316 L stainless steel stents used specifically for intracranial stenosis: Neurolink (Guidant, Advanced Cardiovascular Systems, Inc., Santa Clara, CA), Pharos™ Vitesse™ intracranial stent (Micrus Endovascular, San Jose, CA), and Apollo stent system (MicroPort Medical [Shanghai], Shanghai, China). The periprocedural stroke and death rates were approximately 7% with use of balloon-expandable stents in SSYLVIA[8] and ASSIST[10] trials. However, two other studies identified a slightly higher rate of periprocedural stroke and/or death with balloon-expandable stents compared with self-expanding stents or primary angioplasty.[14,34] A review of 31 studies reporting on 1,177 procedures[21] reported that periprocedural stroke and/or death rates were not different between patients treated with a balloon-expandable stent (n = 906) versus those who had been treated with a self-expanding stent (n = 271; 9.5% vs 7.7%, $P = .47$).

Technique of Prestent Angioplasty

The SAMMPRIS trial also required the prestent angioplasty to be submaximal (nominal diameter of the balloon to be 80% of the target artery). A comparison between submaximal and maximal (nominal diameter of the balloon to be 100% of the target artery) prior to Wingspan deployment demonstrated similar rates of major periprocedural neurological complications (9.0% overall) in one study.[35]

With the current technology, it appears unlikely that use of balloon-expanding stents or maximal prestent angioplasty would have resulted in a lower rate of stroke and/or death in the endovascularly treated patients in the trial.

Periprocedural Antiplatelet Treatment

In the SAMMPRIS, aspirin 325 mg/day (for entire follow-up) and clopidogrel 75 mg/day (for 90 days), were initiated after enrollment. The clopidogrel could be continued beyond 90 days if a cardiologist recommends continuing clopidogrel for a cardiac indication. The duration of clopidogrel use was longer than the 30-day period of administration postprocedure used in the SSYLVIA and Wingspan[9] studies. However, the longer duration of use is unlikely to affect the 30-day postprocedure outcomes. In the ASSIST[10] trial, patients were pretreated with 300-mg aspirin plus 75-mg clopidogrel daily for at least 7 days before the operation. Aspirin, 300 mg/day, was continued for the entire follow-up, and clopidogrel, 75 mg/day, for at least 6 months after stent placement. Probucol, an antioxidation agent that can reduce restenosis after coronary angioplasty, 500 mg twice daily, was started 3 or more days before stent placement and was continued for 6 months or more after stent placement. Intravenous infusion of nimodipine (.6 mg/h) was started 2 hours before the procedure to prevent vasospasm which may reduce the antiplatelet activity of clopidogrel.[36]

Intraprocedural Anticoagulation

There are limited guidelines that address the issue of monitoring the intensity of anticoagulation with various instruments. The joint American College of Cardiology and American Heart Association (AHA) guideline update on percutaneous coronary intervention published in 2005[37,38] indicate that unfractionated heparin is the only anticoagulant for which ACT is used to monitor the intensity of anticoagulation. For coronary interventions, the target ACT recommended is 250 to 300 seconds with the HemoTec® device (Medtronic ACT PLUS®) and 300 to 350 seconds with the Hemochron® device. The National Academy of Clinical Biochemistry guidelines[39] also recommend point of care testing to monitor anticoagulation during percutaneous coronary intervention. Without intravenous platelet inhibitors, ACT targets of >250 seconds with the Medtronic ACTII® or >300 seconds with the Hemochron® FTCA510 tube assay are recommended. i-STAT® device (Abbott Laboratories, Abbott Park, IL) compares well with Hemochron® with a small difference in ACT values and similar values can be used as targets.[40]

In the Wingspan[9] study, a bolus and continuous intravenous infusion of heparin were given before the procedure to raise and maintain the ACT at 2 to 3 times baseline throughout the procedure. In the SSYLVIA[8] trial, heparin was administered to maintain an ACT of 200 to 300 seconds throughout the procedure. Adjunctive drugs such as IIb/IIIa inhibitors were only allowed in patients at high risk for subsequent thromboembolic complications.

The analysis of one study[22] revealed that high dose intraprocedural heparin (an ACT of 250-300 seconds was obtained) and low-dose intraoperative heparin regimen (a lower ACT of 160-220 seconds was obtained) were not associated with different rates of intracranial hemorrhage or stent thrombosis. In the initial 68 patients, heparin was administered intravenously as a bolus of 3,000 U followed by an infusion at 800 U/h to maintain an ACT between 250 and 300 seconds. In the subsequent 101 patients, the heparin bolus and infusion were reduced to 2,000 and 500 U/h, respectively, to maintain an ACT between 160 and 220 seconds, which was the same as that for the protocol of the PROACT (intra-arterial pro-urokinase for acute ischemic stroke) II study.[41] No significant correlation between intraprocedural heparin dose and intracranial hemorrhage was observed after adjustment of the analysis for the potential confounding effect of the stent pattern (a single stent for a lesion vs two stents for a lesion). The ASSIST[10] study used the low dose heparin protocol.

It is important to note that in the Wingspan[9] study, heparin infusion was continued for 24 hours to maintain the ACT value at 2 to 3 times baseline or a partial thromboplastin time at 70 to 90 seconds. In the ASSIST[10] study, heparin was temporarily stopped 3 hours after stent placement to allow removal of the arterial sheath in another 3 hours, and the patient was then switched to subcutaneous low-molecular-weight heparin (Fraxiparine) .4-.6 mL (based on the patient's body weight) every 12 hours for 3 days.

The exact impact of not adjusting target ACT for the instrument (assay) used on the rate of periprocedural stroke and death is not known. It does appear that efforts prior to initiation of the trial to determine the optimal intraprocedural anticoagulation regimen may have impacted the results favorably and should be considered in future trials.

Evolution of Best Medical Treatment

The improvements in institution and effectiveness of best medical treatment are evident from studies conducted in patients with carotid stenosis. A systematic review and analysis of 11 studies[42] found a significant reduction in average annual rates of ipsilateral and any-territory stroke associated with best medical intervention for asymptomatic severe proximal ICA stenosis since the mid-1980s. From 2001, average annual rates of ipsilateral stroke among patients receiving medical intervention alone were below the rates observed in patients who underwent CEA in Asymptomatic Carotid Atherosclerosis Study (ACAS).[43] This reduction was attributable to early initiation of treatment for hypertension and hyperlipidemia with target goals much lower than those use 25 years ago.[42] Furthermore, increasing use of new antiplatelet drugs, blood pressure-lowering drugs such as angiotensin converting enzyme inhibitors and lipid-lowering drugs such as HMG-Coenzyme A reductase inhibitors, has potentially contributed to the observed reduction. Such evolution in best medical treatment alone limits the odds of superiority of interventional treatment in trials such as SAMMPRIS.

Analysis of the Credentialing Criteria Used in SAMMPRIS

Experience Requirements for Treating Interventionalists

The candidate interventionalists for SAMMPRIS submitted procedure note and documentation of outcome from last 20 consecutive intracranial angioplasty and stent cases. The procedures acceptable in order of preference were: Wingspan stent, Neuroform for atherosclerosis, coronary stents for atherosclerosis, angioplasty for atheroclerosis, and neuroform for aneurysms. These 20 cases included a minimum of 3 patients treated with a Wingspan stent in whom the interventionalist personally inserted a stent or performed intracranial angioplasty for intracranial stenosis or used a Neuroform stent (prototype to Wingspan stent) for an intracranial aneurysm. For each case with a complication, the interventionalist had to describe details about the severity of the complication and the setting in which the complication occurred. All procedure notes were reviewed by an independent body of neuro-interventionalists.

Lessons Learned from Carotid Angioplasty and Stent Trials

The variations in credentialing process and impact upon the results of the study have been highlighted before in trials involving comparison between carotid artery stent placement (CAS) and carotid endarterectomy. The Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis (EVA-3S) trial[44] and Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[45] were two trials that provided contradictory results. The 1-month stroke and death rate associated with CAS were prominently higher in the EVA-3S trial compared with the CREST (9.6% and 5%, respectively).

In the CREST, each interventionalist was required to submit data on 10-30 cases previously performed and depending on this data had to perform up to 20 lead-in cases.[46] The Interventional Management Committee (IMC) initiated a review of lead-in case data for each interventionalist, after experienced interventionalists had completed 5 CAS cases and the less-experienced interventionalists had completed 10 CAS cases. Of 427 stent operators who applied for the trial, the IMC did not approve 116 applicants for participation in the lead-in study. The primary reason that approval was not granted was insufficient experience–applicants either did not submit an adequate number of cases or were not the primary operator in the cases submitted. In contrast, EVA-3S required that interventionalists perform at least 12 CAS procedures or at least 35 stent procedures in the supra-aortic trunks, of which at least 5 were in the carotid artery. The study also allowed a new interventional physician to perform stent placement under the supervision of an experienced tutor (a clinician who was qualified to perform stent placement in this study) until he or she became self-sufficient (according to the tutor) and performed a sufficient number of procedures according to the predefined criteria. This contrast in the results of CREST and EVA-3S trials has raised concerns that operator experience could be an important determinant of procedural and trial success.

Operator Experience in Previous Intracranial Stent Studies

Previous trials that resulted in stents being approved under the provision for HDE by the FDA selected centers and operators with considerable experience although no formal criteria were defined. The SSYLVIA[8] trial was conducted in 10 centers in the United States and Europe. Before treating the first patient under the protocol, each interventionalist took part in a didactic and practical training program. The second study conducted in 12 centers in Europe and Asia assessed the safety and performance of Wingspan stent system (Boston Scientific Corporation). An analysis from the NIH Multicenter Wingspan Intracranial Stent Registry compared the rates of 1-month stroke and death in 10 centers that enrolled less than 10 patients and six centers that enrolled more than 10 patients. Completion of a 2-day Boston Scientific training program by the interventionalists at each site was required.

Among low enrolling sites 23% of the treated patients and among high enrolling sites 9% had a stroke or died within 30 days or had a stroke in the territory after 30 days.

Recommendations for Qualification from Professional Organizations

A report of the Practice Guidelines Committee of the American Society of Neuroimaging and the Society of Vascular and Interventional Neurology[47] acknowledged the there are no available data to support specific training requirements for intracranial angioplasty or stent placement. A minimum of 50 procedures requiring microcatheter and microwire placement in intracranial vessels beyond intracranial internal carotid artery or vertebral artery are required to gain expertise in navigating the intracranial vasculature. At least half of them should be performed as a primary operator under supervision. It is also recommended that physicians perform at least 25 endovascular procedures for intracranial stenosis under supervision prior to requesting privileges for performing these procedures. Prior to using specific stents, the recommended training required by manufacturers must be completed. This specific requirement is in addition to meeting the training period and overall case volume requirements set by Accreditation Council for Graduate Medical Education (ACGME) for endovascular surgical neuroradiology residency education. The training period and overall case volume requirements set by ACGME for endovascular surgical neuroradiology fellowship education requires experience in performing at least 100 therapeutic neurointerventional procedures including treatment of occlusive vascular diseases and an accumulated total of 100 diagnostic cervicocerebral angiograms.[48]

The above-mentioned data affirms the value of interventionalist experience in determining the periprocedural rate of stroke and death among patients undergoing intracranial angioplasty and stent placement. The evidence remains insufficient in quantifying the experience required to get beyond the phase of higher risk attributable to the learning curve. The credentialing procedure of CREST and those recommended by professional societies require a higher standard for performance of such procedures. The expected impact of a more rigorous qualification ascertainment process on periprocedural stroke and/or death rate in the patients who underwent intracranial stent placement in SAMMPRIS remains unknown. Further analysis from the SAMMPRIS trial results according to strata based on procedure volumes may help provide a better understanding of the learning curve.

Impact of SAMMPRIS Trial Results on Recommendations From Professional Organizations

The recommendations for intracranial angioplasty and/or stent placement can be divided into two categories: (1) those who considered a role for such procedures in general practice, and (2) those who considered such procedures as experimental procedures. The various guidelines to date may not have shown an evolution in our understanding but rather two different opinions.

Recommendations Supporting a Role in General Practice

A summary of guidelines that consider a role for such procedures in general practice is provided in the subsequent paragraphs. Such guidelines may have to adopt one of the three options: (1) demonstrate that the results of the trial do not apply to all settings and provide a clear description of such settings, (2) recommend continuation of current practice but with local institutional oversight and stringent ascertainment of periprocedural stroke and death, or (3) consider this procedure as experimental and recommend performance only in clinical trials.

The American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, and American Society of Neuroradiology recommended[49] that intracranial angioplasty with or without stent placement should be offered to symptomatic patients with intracranial stenoses $>50\%$ who have failed medical therapy. The societies acknowledge that there is insufficient evidence to make definitive recommendations regarding endovascular therapy in asymptomatic patients with severe intracranial atherosclerosis. Such patients should be monitored for new neurological symptoms, and have periodic noninvasive imaging at regular intervals of 6 to 12 months (magnetic resonance angiography or computed tomographic angiography) initially, and then by cerebral angiography if warranted.

The scientific statement from the AHA Council on Cardiovascular Radiology and Intervention stated that endovascular revascularization by angioplasty and/or stent placement may be considered for patients with symptomatic severe intracranial stenoses ($>70\%$ luminal narrowing) despite optimal medical therapy (class IIb, level of evidence C).[50] Patients with intracranial stenoses should also receive advice about lifestyle modification and treatment of atherosclerotic risk factors with statins, angiotensin-converting enzyme inhibitors, and antithrombotics as recommended by the AHA/American Stroke Association (ASA) guidelines for secondary stroke prevention (class I, level of evidence A).

The consensus conferences on intracranial atherosclerotic disease concluded that no validated criteria exist for selecting patients for intracranial stent placement.[51] However, symptomatic patients with $\geq 70\%$ intracranial stenosis are at high risk for recurrent ischemic events. Similarly, patients with ischemic symptoms that can be attributed to hemodynamic changes appear to have a disproportionately high rate of recurrent ischemic events. Therefore, it is reasonable to consider these patients for endovascular treatment, clinical studies and institutional protocols. In patients being considered for endovascular treatment, special caution is advised for patients with age less than 50 years and those with supraclinoid internal carotid artery stenosis (due to suspected high rate of restenosis). No clear data are available to support the effectiveness of primary angioplasty over stent placement for treatment of intracranial stenosis.

Recommendations Considering Intracranial Angioplasty and/or Stent Placement as Experimental Procedures

A summary of guidelines that consider such procedures as experimental procedures is provided in the subsequent paragraphs. Such guidelines rate intracranial angioplasty and/or stent placement as class IIb (usefulness/efficacy is less well established by evidence or opinion) and level of evidence C (consensus opinion of experts). There appears to be two options

moving forward: (1) The same class and level of evidence would continue until the detailed results of the SAMMPRIS trial are made available; or (2) The recommendations may be changed to class III (conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful) and level of evidence B (data derived from a single randomized trial or nonrandomized studies).

The AHA/ASA guidelines in 2006[52] recommended for patients with hemodynamically significant intracranial stenosis who have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors), the usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain and is considered investigational (class IIb, level of evidence C). The AHA Stroke Council in 2010[53] considered the possibility that stent placement could be associated with a substantial relative risk reduction, but superiority over medical management has not been proved. It is also not clear that stent placement, compared with angioplasty alone, confers any benefit in long-term clinical or angiographic outcome. For patients with stroke or TIA due to 50-99% stenosis of a major intracranial artery, the usefulness of angioplasty and/or stent placement is unknown and is considered investigational (class IIb; level of evidence C).

The Brain Attack Coalition[54] acknowledges the lack of data from large, prospective randomized trials. Intracranial angioplasty/stent placement is considered an optional component for a comprehensive stroke center, although there are selected cases in which such techniques may be of value (grade IVC). If a center does offer this procedure, it is recommended that cases be entered into a registry to track outcomes. It also recommended that if a comprehensive stroke center does not offer extracranial and intracranial angioplasty/stent placement, a referral arrangement to send selected patients to another facility that does offer these interventions must be available.

An assessment by the National Institute for Health and Clinical Excellence (NICE, 2007)[55] concluded: "The evidence on clinical efficacy of endovascular stent insertion for intracranial atherosclerotic disease is currently inadequate and the procedure poses potentially serious safety concerns. Therefore, clinicians should collaborate to organize randomized studies of adequate size to compare endovascular stent insertion for intracranial atherosclerotic disease against best medical management. These studies should clearly define patient selection and be designed to provide outcome data based on follow-up of at least 2 years." The specialist advisors to NICE considered this procedure to be of uncertain safety with potential adverse effects including death, stroke, arterial dissection, vessel occlusion, vessel rupture, hemorrhage, restenosis, and stent thrombosis.

Increasing Emphasis on Quality Assurance Mechanisms

It is likely that intracranial angioplasty and/or stent placement will continue to be offered at most institutions in some limited capacity. However, it would be of paramount importance to ensure that outcomes are tracked and reliably ascertained. Such efforts will ensure certain level of support within the institution and referring facilities. An example of such a model was recently published.[56] The model used two principles: (1) identification of procedure-related adverse events that could be ascertained reliably and reported consistently in previous clinical trials; and (2) determination of the selected procedure-related adverse event rates in previous practice-defining clinical studies. Practice-defining clinical studies were considered to be randomized trials that demonstrated benefit of an endovascular procedure or prospective registries that resulted in approval of an endovascular device by the FDA. Two trials were used to define the selected end-point of any stroke or death within 1 month of the procedure with an acceptable rate of 6.8% (6 of 87 patients recruited in the two trials). The model should be used with the understanding that the estimates are based on patients treated in clinical trials. It has been previously observed that patients recruited in clinical trials have more favorable characteristics than those treated in clinical practice (cherry-picking phenomenon discussed earlier).[7] Therefore, the estimates should be interpreted with this understanding and with appropriate adjustment for clinical severity, if required.

The metrics for measuring quality of care in comprehensive stroke centers proposed by the AHA Special Writing Group of the Stroke Council[57] comment upon intracranial angioplasty and stent placement. The metrics requires ascertainment of percentage of patients undergoing intracranial angioplasty and/or stent placement for atherosclerotic disease with stroke or death within 30 days of the procedure. The end point of any stroke or death within 30 days of the procedure was chosen on the basis of both direct relevance to the procedure and reproducible ascertainment across studies. Patients who undergo these procedures of stenosis with other causes such as vasospasm, arterial dissection, or fibromuscular dysplasia should be excluded from these metrics. Centers should consider tracking these patients separately. Angioplasty and stent placement have become options for treatment of intracranial stenosis both within the context of clinical trials and in clinical practice. Because of the lack of definitive data about the efficacy of intracranial angioplasty stent placement in secondary stroke prevention (class IIb; level of evidence C) and acute ischemic stroke (class IIb; level of evidence C),[58] it is especially important to monitor patients for complications of the procedure.

Regulatory Approvals for Device and Reimbursement

The Wingspan™ Stent System with Gateway™ PTA Balloon Catheter (Boston Scientific SMART, San Leandro, CA, USA) was approved on August 3, 2005[59] by FDA under the HDE program. The current approval is likely to continue. However, reimbursement for the procedure does not exist outside selected settings. It appears unlikely that any of the insurance payers' policies are going to modify the policy to increase coverage for reimbursement after the results of SAMMPRIS trial. The history of reimbursement for performing intracranial angioplasty and/or stent placement is reviewed below.

Effective November 6, 2006,[60] the Centers for Medicare and Medicaid Services (CMS) announced their decision to maintain their position that intracranial angioplasty and stent placement is a promising but unproven therapy. CMS concluded that it "believes the evidence is promising and strongly encourages the development and completion of randomized controlled trials and currently covers angioplasty and stent placement for the

treatment of intracranial artery stenosis ≥50% in patients with atherosclerotic disease when furnished in accordance with the FDA-approved protocols governing category B IDE clinical trials."

Effective January 1, 2006, the American Medical Association (AMA) issued specific CPT® codes for intracranial angioplasty and stent placement procedures.[61] The procedures are currently considered noncovered services by CMS; therefore they are not reimbursed for Medicare patients. However, CMS has published relative value units (RVUs) for these codes as a reference for private payers who decide to cover the procedures so that they can determine appropriate physician payment for intracranial angioplasty and stent placement. The Code Description Published Facility RVUs for 61630 Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous (RVU 35.07), and 61635 Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed (RVU 38.38).

Other health insurers who choose to cover intracranial angioplasty and stent placement cases will reimburse hospitals for inpatient care using a variety of mechanisms including per diems, diagnosis-related groups (DRGs), case rates, or percentage of billed charges. For insurers that use DRG payment systems, reporting the above-described ICD-9-CM diagnosis and procedure codes typically results in assignment to DRGs 533 or 534 (extracranial procedures with and without complications and comorbidities). The results of SAMMPRIS trial is expected to reduce the chances of reimbursement for intracranial angioplasty and/or stent placement and may be the major determinant whether this procedure is continued or not, even in selected settings.

Considertions After SAMMPRIS Trial Results

The following issues need to be considered in the light of the following data:

Intracranial Stenosis Continues to be a Disease without an Effective Method of Reducing the Risk of Stroke and Death

The need for developing new and effective treatments for patients with symptomatic intracranial stenosis cannot be undermined. Patients who have suffered a stroke or TIA attributed to stenosis (50-99%) of a major intracranial artery face a 12-14% risk for subsequent stroke during the 2-year period after the initial ischemic event, despite treatment with antithrombotic medications.[1] The annual risk for subsequent stroke may exceed 20% in high-risk groups.[62] The primary endpoint (ischemic stroke in any vascular territory, intracranial hemorrhage, or vascular death not caused by ischemic stroke) occurred in 22% of the symptomatic patients in WASID.[1] An ischemic stroke in the territory of the symptomatic artery[63] or in any vascular territory occurred in 14% and 19% of the 569 patients, respectively. Sixty of the 77 strokes (78%) happened within the first year. The 1-year risk of stroke in the symptomatic intracranial stenosis territory was 19% for a stenosis ≥70%. Multivariate analysis showed the risk for ipsilateral stroke was highest for a stenosis ≥70%, for patients enrolled early (≤17 days) after qualifying event, and women. The Groupe d'Etude des Stenoses Intracraniennes Atheromateuses symptomatiques (GESICA) study[64] demonstrated a risk of 14% for subsequent stroke among prospectively followed 102 medically treated patients with symptomatic intracranial stenosis over a mean of 23 months. Interestingly, the subsequent combined stroke and TIA was 61% rate (compared to 38% as above) among patients with hemodynamic symptoms.

The Effect of Carotid Stent Placement Trials with Higher than Expected Adverse Events

As the community struggles to understand the implications of prematurely terminated SAMMPRIS trial, the scenario is similar to prematurely terminated EVA-3S trial comparing CAS to carotid endarterectomy. The EVA-3S trial started recruiting in November 2000.[65] In January 2003, the safety committee recommended mandatory use of distal protection devices because of a higher risk of stroke in patients treated without distal protection. Although initially recruiting patients with stenosis of ≥70%, the trial started recruiting patients with stenosis of ≥60% in October 2003. In September 2005, the safety committee recommended stopping enrollment after 527 patients (intended target recruitment of 872 patients) had been randomized. On the basis of the observed 30-day risk of stroke or death after endarterectomy, more than 4,000 patients were required to test the noninferiority of stent placement. Given the observed 30-day risks of CAS, the committee considered it to be extremely unlikely that the trial would reach its objectives despite further enrollment. The 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after CAS. The rate of disabling stroke or death was 1.5% and 3.4% after endarterectomy and CAS, respectively. At 6 months, the incidence of any stroke or death was 6.1% and 11.7% after endarterectomy and CAS, respectively. However, continuation of further trials such as the CREST[45] comparing CAS and endarterectomy demonstrated different results. Among 2,502 patients over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the composite primary outcome of stroke, myocardial infarction, or death between the CAS group and the endarterectomy group (7.2% and 6.8%, respectively; $P = .51$). The evolution of CAS suggests that a single trial cannot be used to discontinue efforts directed toward determining the effectiveness of a new procedure. However, such information should be used to modify the design of future trials.

However, the difference in scenario was that the results of EVA-3S appear somewhat contradictory to the existing data derived from other studies. A randomized trial compared CAS with the use of a distal protection device to endarterectomy in 334 high surgical risk patients with either a symptomatic carotid-artery stenosis of ≥50% or asymptomatic stenosis of ≥80%.[66] The primary end point of death, stroke, or myocardial infarction within 30 days or ipsilateral stroke between 31 days and 1 year occurred in 12% of the patients assigned to undergo CAS and in 20% of patients assigned to undergo endarterectomy. Several registries such as Boston Scientific EPI: A Carotid Stenting Trial for High-risk Surgical Patients (BEACH),[67] Carotid Artery Revascularization Using the

Boston Scientific EPI FilterWire EX and the EndoTex Nexstent (CABERNET),[68] Acculink for Revascularization of Carotids in High-Risk Surgical Patients (ARCHER).[69] Medtronic AVE Self-expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis (MAVERIC),[70] and Carotid RX ACCULINK/ACCUNET Postapproval Trial to Uncover Unanticipated or Rare Events (CAPTURE),[71] had demonstrated low rates of adverse events in large number of patients treated with CAS using reliable methodology of data ascertainment and collection. Intracranial angioplasty and/or stent placement does not have other supporting data and on-going trials posing a greater challenge for avoiding premature discontinuation of efforts in this area.

The Prerandomization Assessment Lessons from Percutaneous Transluminal Coronary Angioplasty and Stent Placement

A critical evaluation of percutaneous transluminal coronary angioplasty (PTCA) and stent placement suggests that the approach prior to randomized trials was more rigorous and had provided a better understanding of adverse rates and operator experience than the approach seen with intracranial angioplasty and stent placement. PTCA was introduced in 1977[72] and in March 1979, the National Heart, Lung, and Blood Institute (NHLBI) established an international registry of PTCA treated patients to evaluate the safety and efficacy of this new procedure and to record the learning experience.[73,74] The registry collected cases prospectively beginning in 1979, as well as retrospectively back to the advent of the procedure in 1977. To participate in the registry, centers were required to submit data on all patients who had had a guide catheter introduced as the first step in the angioplasty procedure. From 1979 to 1981, 3,248 patients were entered from 105 clinical sites. In late 1981, the registry stopped entering new cases and shifted its efforts toward postangioplasty follow-up. Sixteen of the largest centers, capable of complete follow-up, participated in this 5-year follow-up phase. The complications were defined according to the PTCA Manual of Operations. The registry also analyzed the rate of all complications and the rate of major complications (death, myocardial infarction, or emergency surgery) by the sequence of performance. The number of procedures performed were divided into strata of first 10 cases, second 10 cases, and onwards. These groupings were then related to the complications.

In 1993, the FDA granted approval for the use of the Gianturco–Roubin stent (Cook Cardiology) for treatment of acute or threatened closure during coronary intervention. In 1994, the Palmaz–Schatz balloon-expandable stent (Cordis Corporation) was approved by the FDA for primary treatment,[75,76] The Working Group on Coronary Circulation[77] reviewed the successful approval of these stents and recommended clinical evaluation under restricted availability in a minimum of 100 patients with predefined data recorded and monitored by an independent core laboratory based on this experience for future trials. Whenever a new stent is being introduced for clinical application, a registry of the 1-year clinical outcome in the first 300-400 patients (including the cases involved in presale phase) should be organized by the company and the results made available.

For example, the Palmaz–Schatz was made available to selected centers under strict research regulations.[78] A total of 226 patients were enrolled prospectively and consecutively into this multicenter study from December 1987 to September 1989. All United States centers participating in the stent (Johnson & Johnson, Warren, NJ, USA) followed the protocol under the specific indications for use as outlined in the investigational device exemption, approved by the FDA. At that time over 225,000 procedures primary angioplasty procedures were being performed per year.[78] The inclusion and exclusion criteria were specified and protocol for stent deployment and antithrombotic treatment were prespecified. Patients were seen at 2 weeks, and 1, 2, and 3 months. Quantitative coronary analysis was performed with the use of a computer-based coronary angiography analysis system with automatic edge detection (ADAC, Milpitas, CA, USA) and then reviewed by three observers. Technical success tended to improve with operator experience, ranging from 89% in the first 50 patients versus 98% in the last 50 patients who underwent stent placement. The SAMMPRIS trial relied on data derived from the NIH Multicenter Wingspan Intracranial Stent Registry, which lacked the quality parameters for data ascertainment and collection seen in PTCA and coronary stent studies.

The Next Step After SAMMPRIS Trial Results

The medical professionals involved in the care of patients with intracranial atherosclerosis will have to decide whether they want to continue offering the procedure in selected patients. If the community chooses to continue the procedure in perhaps a more restricted manner, the first step would be to create a prospective registry with standardized data collection forms and monitoring by a data coordinating center. The registry should focus on analyzing the rate of all complications and the rate of major complications (stroke and death) and attempt to register data up to 6 months postprocedure. Participation in such a registry ensures internal quality control and provides an opportunity to objectively assess the operator experience and periprocedural aspects of the procedure. More specifically, data collected within a well-designed registry will allow assessment of the learning curve for operators, identification of clinical and angiographic prognostic factors with prevalence that predispose to imbalances between treatment groups, ascertainment of device performances within various strata based on angiographic features, identification of technical factors that may influence outcome of procedures, and optimal antithrombotic regimen in the periprocedural period. Participation in such a registry also reduces medico-legal liability for the operator and ensures support from peers.

The consent forms for the procedure either as part of the registry or outside the registry would require clear documentation that the patient or legally authorized representative was informed regarding the results of the SAMMPRIS trial and the reasons for expected benefit of intracranial angioplasty and/or stent placement to the consenting party. An objective and reliably ascertained periprocedural rate of stroke and death at the local institution can be invaluable during the consenting process.

The medical community would have to decide whether enough justification exists to consider evaluation of primary angioplasty as a treatment modality for symptomatic patients with intracranial stenosis. A phase II single arm futility design maybe necessary to accrue appropriate data prior to proceeding to a larger scale.[79] Such an approach requires comparison of proportion of favorable outcomes in the single arm intervention to prespecified stopping criteria. If the proportion of favorable outcomes were less than the prespecified stopping criteria, an approach such as angioplasty would be considered not sufficiently effective to warrant further evaluation in phase III trials.

Members of the writing group are of the opinion that SAMMPRIS trial was "reasonably" explanatory. The data supports modification but not discontinuation of our approach to intracranial angioplasty and/or stent placement for intracranial stenosis. The optimal method to avoid premature discontinuation and without exposure of patients to excessive risk is to proceed with another clinical trial with appropriate modifications in design based on lessons learned from the SAMMPRIS trial.

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